Subcutaneous Allergen Immunotherapy (SCIT)

by the AAAAI Immunotherapy Committee
Presented by Shashank Sheth, MD

© AAAAI Revised 2006
NO FINANCIAL RELATIONSHIPS TO DISCLOSE
Objectives

• To discuss indication and benefits of allergy immunotherapy (SCIT)
• To discuss risks associated with SCIT
• To review guidelines and discuss practical points for office administration of SCIT
Allergy Immunotherapy

- The repetitive administration of specific allergen(s) to patients with defined IgE-mediated conditions for the purpose of developing tolerance to the potential inflammatory effect upon re-exposure to those allergen(s)
Indications

• Indicated for management of IgE mediated disorders:
  – Allergic rhinoconjunctivitis
  – Allergen-induced asthma
  – Hymenoptera hypersensitivity

• Not indicated for:
  – Food allergies
  – Urticaria / angioedema
  – Disorders that are not IgE mediated
Factors to Consider When Prescribing Immunotherapy

– Effectiveness of medications and avoidance measures
– Side effects/costs of medications vs. immunotherapy
– Possible special benefit in children as preventative therapy for asthma
– Patient adherence to medication and recommendations
– History of systemic reaction to Hymenoptera sting (children < age 16 with systemic reaction other than that limited only to the skin)
Who Is Not a Candidate for Immunotherapy?

- Relative contraindications for AIT:
  - Significant immunodeficiency
  - Malignancy
  - Severe psychological disorders
  - Poor compliance with medications
  - Treatment with beta-blockers (including topicals)
  - Severe obstructive lung disease (limited reserve)
  - Conditions that contraindicate epinephrine

- Exceptions for hymenoptera venom therapy
  Theodoropoulos DS and Lockey RF  *Allergy Asthma Proc*  2000; 21:159-166
Studies Defining Benefit of Immunotherapy for Allergic Rhinitis

Malling HJ Allergy 1998; 53: 461-72
Dust Mite Immunotherapy Trials for Asthma

- Significant decrease in asthma symptoms
- Decrease in asthma medications
- Decrease in mite-specific immediate and late phase reactions

Aas K. *Acta Paediatr Scand* 1971; 60: 264-268
Cat Immunotherapy Trial

• Double-blind, placebo controlled
• Decrease in specific and non-specific bronchial sensitivity
• Decrease eye, nasal and asthma symptoms with cat challenge/exposure
• Improved asthma control

Haugaard L, Dahl R *Allergy* 1992; 47: 249-254
Secondary prevention

• Des Roches et al. conducted a trial on children age 3 to 6 who were monosensitized to house dust mite
  – Those who were treated with specific immunotherapy were significantly less likely to develop sensitization to additional allergens over the next 3 years compared to those who did not receive IT

Immunotherapy Prevents the Development of New Allergen Sensitizations

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>None</th>
<th>Cat</th>
<th>Dog</th>
<th>Alternaria</th>
<th>Grass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy</td>
<td>22</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Control group</td>
<td>22</td>
<td>0</td>
<td>12</td>
<td>8</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

### Improvement in Medication Requirements and Symptom Scores After Immunotherapy

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Dust mite (Odds Ratio)</th>
<th>Other allergens (pollen, mold, dander) (Odds Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom improvement</td>
<td>2.7 (1.7 – 4.4)</td>
<td>4.8 (2.3-10.1)</td>
</tr>
<tr>
<td>Reduction in medication</td>
<td>4.2 (2.2-7.9)</td>
<td>ND</td>
</tr>
<tr>
<td>Decreased bronchial hyperresponsiveness</td>
<td>13.7 (3.8-50)</td>
<td>5.5 (2.8-10.7)</td>
</tr>
</tbody>
</table>

Estimated Costs of Treatment of Allergic Rhinitis

<table>
<thead>
<tr>
<th>Treatment Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total 5 Year Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy (single injection)</td>
<td>$800</td>
<td>$290</td>
<td>$290</td>
<td>$290</td>
<td>$290</td>
<td>$1960</td>
</tr>
<tr>
<td>Medications (oral &amp; topical)</td>
<td>$1200</td>
<td>$1200</td>
<td>$1200</td>
<td>$1200</td>
<td>$1200</td>
<td>$6000</td>
</tr>
</tbody>
</table>

Bernstein JA. Pharmacoeconomic considerations for allergen immunotherapy Clin Allergy Immunol. 2004;18:151-64
Indications for asthma in children

- Allergic asthma only when allergic component is well documented
  - Not a substitute for avoidance of environmental allergens
  - May be used in addition to environmental control and pharmacotherapy if control suboptimal
  - Not recommended when asthma is unstable

Becker et al. JAMC 173 (6); S46-49.
Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy

<table>
<thead>
<tr>
<th>Pollen Count (grains/m$^3$)</th>
<th>Initial Placebo Trial</th>
<th>Current Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Score</td>
<td>Study group</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td></td>
<td>Immunotherapy</td>
<td>Maintenance</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Discontinuation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None (control)</td>
</tr>
</tbody>
</table>

May June July Aug 1989
May June July Aug 1993
May June July Aug 1994
May June July Aug 1995

PAT Study

• European study that evaluated 205 children at 6 centers with grass or birch allergy and no history of asthma

• Randomized to 2 groups
  – IT for 3 years
  – Open control groups

• Conclusion: IT can reduce development of asthma in children with seasonal rhinoconjunctivitis

Moler et al J Allergy Clin Immunol 109 (2); 251-256. 2002
Preventative Therapy in Children

Odds ratio of developing asthma in those without immunotherapy at 5 years was 2.68 (1.3-5.7)

Insect Venom IT Efficacy

• Prospective uncontrolled trials of bee and vespid IT:
  – 0-9% of vespid-allergic had systemic reactions
  – 20% of bee-allergic had systemic reactions
    • Milder reactions

• VIT
  – Prevents systemic reactions in 95% of treated patients
  – Treatment failures and fatalities in patients with systemic mastocytosis

Bonifazi et al. Allergy 2005: 60 (1459-1470)
VIT for 1-2 yrs: relapse rate 25% immediately

VIT for 5 yrs: relapse rate < 20% after 15 years

FIG 3. Natural history of insect sting allergy showing the risk of systemic reaction to a sting in untreated patients (solid line) and in patients who received VIT (dashed lines) for a duration of either 1 to 2 years or for a mean of 6 years. Reprinted with permission from Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. J Allergy Clin Immunol 2000;105:389.
Allergen Immunotherapy: Local Reactions

• Local reactions: redness, swelling and heat at injection site
  – Common occurrence
  – Large local reactions not predictive of future systemic allergic reactions

• If persistent large local reaction consider:
  – Pre-medications with H1 blockers
  – Decreasing dose or rate of build-up for patient comfort
Signs and symptoms can include:
- Urticaria, angioedema
- Increased respiratory symptoms (nasal, pulmonary or ocular)
- Gastrointestinal and/or uterine cramping
- Hypotension

Onset usually rapid (majority occurring within 30 minutes) although delayed reactions (hours) reported often

Low incidence (< .05% to 3.5% of injections)
Immunotherapy: Systemic Reactions

- Factors that may increase risk of systemic reaction include:
  - Symptomatic asthma
  - High degree of allergen hypersensitivity
  - Use of beta-blockers (possibly ACE inhibitors)
  - Dosing error
  - Injection from new vial
  - Injection given during period of allergy symptom exacerbation
Just How Frequent Are Systemic Reactions?

- 0.51% of all injections may produce a systemic reaction
- 45% of reactions occur in patients who have had previous systemic reactions
  Matloff SM et al. *Allergy Proceed* 1993; 14: 347-350
- 125 systemic reactions in 109 patients (out of 1506 receiving immunotherapy)
- Overall, incidence of 1 reaction per 1831 injections
- 0.8% to 46.7% (mean 12.92%) systemic reaction rate for conventional schedule
- 0.05% to 3.2% rate per injection for conventional
  Stewart GE and Lockey RF *J Allergy Clin Immunol* 1992; 90: 567-78
Should I Be Aware of Delayed Systemic Reactions?

- **32% occurred after 30 minutes and 8% of reactions occurred after 2 hours**
  Matloff SM et al. *Allergy Proceed* 1993; 14: 347-50

- 38% (52 reactions) occurred 35 minutes to 6 hrs
- Most common reactions pruritis and urticaria
- Pollen extracts associated with reactions
  Greenberg MA et al. *J Allergy Clin Immunol* 1986; 77: 865-70

- 68% of systemic reactions were delayed (>20 minutes) – fortunately majority were minor (rhinitis)

Weldon D Abstract Aspen Allergy Conference, 1997
What Types of Reactions Should I Anticipate?

- No one has a crystal ball – anticipate anything
- Local reactions are very insensitive predictor of subsequent systemic allergic reactions
  
  **Tankersley MS et al. J Allergy Clin Immunol 2000; 106: 840-3**

- 52.8% cutaneous only, 12% respiratory, 30.4% respiratory and skin, and 4% anaphylaxis
  

- 17% of systemic reactions judged to be severe
  
  **Matloff SM et al. Allergy Proceed 1993; 14: 347-350**
Treatment of Allergen Immunotherapy Systemic Reactions

- Aqueous epinephrine 1:1,000 is the standard of care
- IM epinephrine if systemic reaction
  - Adults: 0.3ml to 0.5ml q5 minutes up to 3 times
  - Children: 0.01ml/kg body weight q5 minutes up to 3 times (Then consider more aggressive measures)
- Supine position
- Tourniquet
Treatment of Systemic Allergic Reactions

- H1 antihistamines: diphenhydramine IM or IV – Adults: 25 to 50 mg Children: 1-2 mg/kg
- H2 blockers p.o. or IV (cimetidine, ranitidine, famotidine) – for epinephrine – resistant hypotension or erythroderma
- Oxygen and bronchodilators
- Intravenous fluids or vasopressors as needed for vascular collapse
- Depending upon the reaction, consider po or IV steroids (prednisone)
Systemic Reactions

• May vary from mild to severe
• DO NOT DELAY GIVING EPINEPHRINE!!!
• Antihistamines and oral corticosteroids are second lines of treatment
• Maintenance dose may have to be reduced
• Re-evaluate risk/benefit ratio of IT
What About Immunotherapy Outside of the Prescribing Allergist’s Office

- “The standard of care concerning the administration of immunotherapy should be the same regardless of where the immunotherapy is given and the specialty of the supervising physician.”
- Medical facilities should have:
  - Stethoscope and sphygmomanometer
  - Tourniquet and large bore needles
  - Aqueous epinephrine HCl 1:1000
  - Equipment to administer oxygen by mask
  - Intravenous fluid set-up
  - Antihistamines, corticosteroids, and vasopressor (for injection)

Position Statement on Administration of Immunotherapy Outside of the Prescribing Allergist Facility ACAAI Board of Regents April 25, 1998
Fatal Reactions

• Study of reactions from 1990-2001
  – 20 fatalities due to IT directly reported
  – 21 fatalities due to IT indirectly reported
  – 1 fatality due to skin testing
  – 273 practice entities reported near-fatal reactions
  – Incidence of fatal reactions:
    • 1 per 2,540,000 to 6,850,000 injections

Fatalities

• 3.4 fatal immunotherapy reactions per year
• Only 25 % survey response – underestimate
• None of the patients were receieveing beta-blockers
• Majority of fatalities were during maintenance therapy

Delayed and Biphasic Reactions

• Some studies found delayed reactions – wheezing or urticaria; none were severe

• Biphasic reactions are rare, but usually less severe than additional reaction
  – May occur up to 24 hours after complete resolution of initial reaction
Practical Points

- Withhold allergy shots for acute asthma symptoms
  - Thorough lung exam prior to shot and 30 minutes after shot
  - Consider measuring peak flow prior to shot
Mixing Allergen Extracts

• Some allergen extracts contain proteases
  – May degrade proteins in other extracts
  – Most notable in mold and whole body insect

• Glycerin
  – Diluent that inhibits protease activity
  – Causes more pain at injection site
Lingo

• Extract potency is measured as:
  - BAU – bioequivalent allergy unit
  - AU - allergen units
  - Wt/vol – weight-to-volume
    • Weight in grams per volume in mL (ie- 1:100 means 1 gram of dry allergen was added to 100 cc of buffer)
  - PNU – protein nitrogen units
    • 1 PNU = 0.01 g protein nitrogen

• Standardized extracts
  - Consistent potency
  - Decreased risk of adverse reaction

• Non-standardized extracts
  - Wide-range of potency
  - Wt/vol or PNU
Storing and Handling

• Once an extract is prepared for administration, it is subject to loss of potency
  – More likely in dilute concentrations
  – Preservatives
    • 0.03% human serum albumin
    • 10% – 50% glycerin

• High temperatures weaken potency
  – Keep extracts in refrigerator at all times
  – 4 degrees Celsius

Prescription Schedule

• Build-up Phase (4 – 6 months)
  – Starting Dose
    • Usually 1,000- or 10,000-fold dilution of maintenance concentrate
    • If extremely sensitive by history or skin test, then start with an even smaller dose
  – Frequency
    • Initially once or twice a week
    • Then weekly, and then biweekly
  – Volume
    • Start at 0.05 mL
    • Usually increased by 0.05 mL to 0.1 mL per injection

http://www.jcaai.org/pp/ai_12_schedules.asp
Prescription Schedule

• Maintenance
  – Intervals can be spaced to 4-6 weeks
  – Should be individualized to patient with regards to efficacy and safety
  – Clinical improvement should be seen within one year of starting maintenance therapy
    • If not, re-evaluation and possible discontinuation should be considered
Assessment

• Clinical parameters
  – Symptoms scores
  – Medication use

• Periodic skin tests and in vitro IgE
  – Not recommended routinely

http://www.jcaai.org/pp/ai_12_schedules.asp
Duration of IT

• No definite guidelines
• General consensus
  – Patient is symptom free or has substantially reduced symptoms for 1 – 2 years
  – 3 to 5 years
• Venom IT may be continued lifelong in some patients
Immunotherapy has been associated with all of the following except:

- A. suppression of early and late responses to allergen challenge
- B. improvement in symptoms for 6 to 12 months after treatment cessation, followed by relapse
- C. reduced progression from allergic rhinitis to asthma in children
- D. protection from anaphylaxis to bee stings
Injection Technique

• 26-27 gauge syringe with ½ or 3/8 inch nonremovable needle

• Antigens from different vials should not be combined into a single syringe

• Injection to be given subcutaneously so that there is slow absorption
  – Rapid absorption (IM injection) could increase risk of systemic reaction
Injection Technique

• Injection to be given in posterior portion of middle third of the upper arm at junction of deltoid and triceps muscle
• Depress plunger at a rate that does not lead to a wheal formation or excessive pain
• Apply mild pressure to site with gauze for ~1 minute
• Do not massage site – this may increase rate of absorption
Injection Technique

• Reassess patient after at least 30 minutes of waiting
  – Subjective assessment
  – Lung exam
  – Document size of local reaction – wheal and flare
Prescribing Immunotherapy

- Patients should be informed of risks and benefits of immunotherapy
  - Informed of all alternative options
  - Informed consent signed
  - Patients should be informed of what to do in case of emergency after injection

- Due to the risk of severe systemic reactions (including death), immunotherapy should be administered only in a physician’s office equipped to handle anaphylaxis
IT in Pregnancy

• Two studies of total 200 pregnant patients on IT
  – No increase in prematurity, toxemia, abortion, neonatal death, or congenital malformations

• One case report of a miscarriage from a systemic anaphylactic reaction

• General guidelines
  – Continue IT during pregnancy but do not increase dose
  – Do not initiate IT while patient is pregnant
Other Issues to Consider

• “Summary Statement 51: Immunotherapy injections should not be administered at home because of the risk of inadequate recognition and treatment of systemic reactions.”
• “Patients at high risk for systemic reaction should receive immunotherapy in the office of the physician who prepared the patient’s vaccine”

Summary

• Immunotherapy has been shown to be effective in:
  – Asthma
  – Allergic rhinitis
  – Stinging insect anaphylaxis

• Effectiveness of immunotherapy depends on appropriate dose and duration of immunotherapy treatment

• Systemic reactions to immunotherapy are rare but can be life-threatening
  – Appropriate training of staff and medication should be available to treat serious reactions